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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
WALICKA, M	
ART UNIT	**PAPER NUMBER**
1652	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/601,138	Applicant(s) FOGH ET AL.	
	Examiner Malgorzata A. Walicka	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 35-46* is/are pending in the application.

4a) Of the above claim(s) *38-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The examiner is acknowledging the preliminary amendment filed on Oct. 26, 2000, paper No. 5a. The amendments to the specification and claims have been entered. Claim 33 and 34 have been cancelled.

The Response to "Sequence Listing " Requirement filed on September 13, 2001, paper No. 11b, is also acknowledged. All amendments to the specification have been entered. The previously submitted Sequence Listing was substituted with the newly filed.

Election of claims, paper No. 8, filed May 9, 2001 is acknowledged. Applicants elected, with traverse, invention of Group I, claims 1-37 drawn to the direct enzyme therapy. In response to the requirement of the species election Applicants elected species No. 1, acute intermittent porphyria (AIP) and the respective involved enzyme porphobilinogen deaminase (PBGD), with traverse.

Detailed Office Action

1. Election/Restriction

1.1. Invention election

The traverse is on the ground that the claims relates to treatment of a disease caused by deficiency of an enzyme belonging to the heme biosynthetic pathway and the distinction here is between the (I) therapy by supplying the enzyme directly, and (II) therapy by supplying the enzyme indirectly by providing expressible DNA encoding that enzyme. Furthermore, Applicants state: "The Examiner concedes that PCT unity rules apply."

The examiner, in her restriction requirement wrote: "The inventions listed as group I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features. " The examiner indicated that both methods of treatment are different. Applicants are reminded that the enzyme and the encoding gene do not consist a contribution over the prior art. From the Applicants' information disclosure statement one may learn that the gene was cloned as early as in 1986, therefore, the inventions set forth in the claims have no special technical feature and encompass two different methods of use of the gene and enzyme. 37 CFR 1.475 does not provide for multiple products or **methods** within a single application and therefore unity of invention is lacking with regard to Groups I-II. The requirement of restriction is proper and made FINAL.

1.2. Species election

The traversal is on the ground that "generic claims are allowable, see MPEP 809.02"; further, applicants state "At least claims 1, 5-20, 22-32 and 35 are generic."

The Applicants' attention is drawn to the fact that MPEP 809.2(a) rules: "Where generic claims are present, the examiner should send a letter including only a restriction requirement or place a telephone requirement to restrict." In addition, this is the national stage of a PCT application and Applicants did not pay additional examination fees for more than one species to be examined.

The are directed to the following:

1. acute intermittent porphyria (AIP) and porphobilinogen deaminase (PBGD)
2. ALA deficiency porphyria (ADP) and ALA dehydratase,
3. porphyria cutanea tarda (PCT) and uroporphyrinogendecarboxylase,
4. hereditary coproporphyria (HCP) and harderoporphyria (HDP) and coproporphyrinogen oxidase,
5. variegata porphyria (VP) protoporphyrinogen oxidase,
6. congenitial erythropoetic porphyria (CEP) and uroporphyrinogen III synthase,
7. erythropoetic protoporphyria (EPP) and ferrochelatase,
8. Hepatoerythropoetic porphyria (HEP) and uroporphyrinogen decarboxylase, or

enzymatically equivalent parts or analogues thereof.

Each of the above 8 species relates to a distinct clinical syndrome and underlying deficiency of a specific enzyme in the eight step synthesis of heme. The deficiency in two diferent syndromes hereditary coproporphyria (HCP) and harderoporphyria (HDP) seems to be related to defects in one enzyme, coproporphyrinogen oxidase, yet molecular genetics of both syndromes may be not well characterized at this moment.

Thus, each of the species has a special technical feature determined by the deficiency of the specific enzyme.

In her restriction requirement the examiner indicated that more than "At least claims 1, 5-20, 22-32 and 35 are generic."

GROUP I

Species 1

Claims 4, 36, 37

Species 2-8

No specific claims

Generic claims: 1, 2, 3, 5, 6, 7, 1, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 35

Group II

Species 1

Claims 38, 40, 41, 42, 43, 44, 45, 46

Species 2-8

No specific claims

Generic claim: 39

Requirement of the species election is proper and made FINAL.

2. Objections

2.1 Drawings

This application has been filed with informal drawings; see the copy of notice of draftsperson's. The drawings are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

3. Rejections

3. 1. 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-32 and 35-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rejected for the use of the terms:
(1) enzymatically equivalent part thereof, and
(2) analog.

The term enzymatically equivalent part of the enzyme is indefinite. For examination purposes it is assumed that "enzymatically equivalent part" means enzymatically active fragment.

The meaning of the term analog is exemplified on page 7 line 12, but the disclosure fails to define the term.

Claim 20 is indefinite because it recites the phrase "at least part of its enzymatic activity." The phrase ""at least part of its enzymatic activity" is a relative phrase that is not defined by the claim; the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus the claim is indefinite.

Claim 20 also recites the term "intracellularly." Because neither the claim nor the specification defines the meaning of the term, it is not clear whether the term means the interior of any cell in the patient's body, interior of any cell that does not belong to the vasculature, or something else. Thus the claim is indefinite.

Claim 23 recites the phrases "tagged with specific carbohydrates" or "other liver cell specific structures" that render the claim indefinite. Neither the

claim nor the specification defines the meaning of the phrases; therefore the one skilled in the art does not know what Applicants regard as the invention.

3.2. 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Lack of written description

Claims 17 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to method for treatment or prophylaxis of a disease caused by deficiency of an enzyme belonging to the heme biosynthesis pathway, the method comprising administering an effective amount of a catalyst or an enzymaticaly equivalent part or analogue thereof when:

(1) in claim 17 the catalyst's half-life in the blood stream is enhanced,
(2) in claim 19 the catalyst is complexed with a heavy metal,
(3) in claim 21 the catalyst is a small artificial enzyme or an organic catalyst that can polymerize porphobilinogen to hydroxymethylbilane,
(4) in claim 22 the catalyst is formulated in such a manner that it exerts its activity intracellularly.

Neither claim 17 nor the specification described the manner of the prolongation of the catalyst half-life in the blood stream. Several methods of protein modification or coating may be use for that purpose, but Applicants disclose none.

The examiner acknowledges that Applicants mention on page 13 of the specification "a heavy metal" and "a small artificial enzyme or an organic catalyst." However, neither claim 19 or the specification name any specific metal with which the catalyst is to be complexed, nor the way in which complexing is to be performed. Claim 21 and the specification do not describe any small artificial enzyme or any organic catalyst that can polymerize porphobilinogen to hydroxymethylbilane.

Also, neither claim 22 nor the specification described the manner of formulation of the catalyst so that it exerted at least part of its enzymatic activity intracellularly upon administration to the subject.

The disclosure fails to sufficiently describe the inventions claimed in claims 17, and 19-22 in such full, clear, concise, and exact terms. The specification refers to the enhancement of the catalyst's half-life only on page 13 line 14: "The formulation is preferable one which is able to enhance the half-life

of the catalyst in the subject' blood stream. This **may be use** of a formulation wherein the catalyst has a polyetylene glycol coating." Therefore the applicants do not described the applied method but suggest the method. Further, also on page 13, line 17 Applicant just state that "The catalyst **may also** be complexed with **a heavy metal**." Further on page 13 line 21 Applicants state that part of the enzymatic activity may be exerted intracellularly. "This may be when the catalyst is a small artificial enzyme or an organic catalyst which can polymerize porphobilinogen to hydroxymethylbilane." However, Applicants even do not exempyfy such a catalyst. As to the catalyst formulated in such a manner that it exerts its activity intracellularly, Applicants just state on page 13 line 26 "Furthermore, **the catalyst may be said enzyme** formulated in such a manner that it exerts at least part of its enzymatic activity intracellularly upon administration to the subject."

The examiner concludes that the above quoted sentences that are the only references to the claimed invention one may find in the application, merely express Applicants' wishes and do not consist an enabling description of the claimed invention. A skilled artisan would not recognize the Applicants were in possession of the claimed inventions

Applicants are referred to the revised interim guidelines concerning compliance with the written description requirement of 35 USC section 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

3.2.2. Scope of enablement

Claims 1-20, 22-31, 32 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method for treatment or prophylaxis of acute intermittent porphyria (AIP) by administering to the subject an effective amount of porphobilinogen deaminase (PBGD) does not reasonably provide enablement for the method to treat any disease caused by deficiency of at least eight other enzymes belonging to the heme biosynthetic pathway, when the enzyme originate from any biologic or man-made source or is an enzymatically active fragment or analogue thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the treatment of eight human clinical conditions with huge number of all known and unknown enzymes of the heme biosynthetic pathway from all existing organisms as well as engineered. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative

skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses methods of treatment of any of eight human clinical conditions with huge number of all known and unknown enzymes of the heme biosynthetic pathway from all existing organisms as well as engineered. While methods of gene cloning and expressing, as well as testing different enzymatic activities are well known in the relevant art and skills of the artisans are highly developed, screening of an extremely large number of known enzymes of the heme biosynthetic pathway for its use in eight human clinical conditions, as well as screening genomic and cDNA libraries from all organism and man-made for the DNAs encoding any enzymes of the heme biosynthetic pathway that are unknown, expressing and isolating these enzymes and using them for treatment of subject in need is not within the realm of routine experimentation.

The working examples provide the guidance only for the method to treat AIP with PBGD. The examiner finds that one skilled in the art would require additional guidance such as defining the species of the disease selected form the group of ALA deficiency porphyria (ADP), porphyria cutanea tarda (PCT, hereditary coproporphyria (HCP)and harderoporphyria (HDP, variegata porphyria, congenitial erythropoetic porphyria (CEP), erythropoetic protoporphyria (EPP), hepatoerythropoetic porphyria (HEP) and the enzyme involved. Without such guidance, the experimentation left to those skilled in the art is improperly extensive and undue.

3.3. 35 USC, section 103

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-32 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raich et al. "Molecular cloning and complete primary sequence of human erythrocyte porphobilinogen deaminase " (*Nucleic Acid Research*, 1986, 14, 5955-5698) and further in view of many publications on enzyme replacement therapy, for example Beutler E. et al, "Enzyme replacement therapy for Gaucher Disease" (*Blood*, 1991, 78, 1183-1189).

The claims of the instant application are directed to the enzyme replacement therapy of acute intermittent porphyria a genetic disease in which the porphobilinogen deaminase is defective.

The PBGD gene has been cloned and sequenced for the first time by Raich et al. Raich et al teach that deficiency of PBGD is responsible for the

disease AIP. However Raich et al do not teach enzyme replacement therapy with PBGD in AIP cases.

Beutler et al teach that the enzyme replacement therapy has been very succesful in treating patients suffering from another genetic defect manifested as Gaucher disease.

It would have been obvious to one having ordinary skill in the art at the time of the invention to express the gene taught by Raich et al, to obtain PBGD protein and administer it to the subject having the defective form of the enzyme, similarily as taught by Beutler et al in case of Gaucher disease.

The motivation would be, in the light of long felt need, to provide a treatment of AIP that is more efficient than the methods used thus far. The expectation of success is also provided by Beutler et al who teach that the enzyme replacement therapy results in marked regression of pathologic changes and general improvement in patients' health.

Claims 2-5, dependent on claim 1, enunerate the syndroms and enzymes, defficiencies of which cause them. The other dependent claims, claims 6-25 and 28-32 are directed to standard methods of pharmaceutical treatment as applied to the treatment of AIP subjects with porphobilinogen deaminase. Claim 27 is directed to the chemical synthesis of the porphobilinogen deaminase. Independent claim 26 is directed to the recombination method of synthesis of the porphobilinogen deaminase. Dependent claim 35 is directed to the recombinant form of the enzyme and claims 36 and 37 indicate DNA sequences encoding the enzyme of the claimed method and pharmaceutical composition. Thus, none of the dependent and independent claims is novel and nonobvious over the prior art.

4. Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

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